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09/498,046	02/04/2000	Sabine Neirynck	VIB-08	8244

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	25

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,046	NEIRYNCK ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/4/2, 11/12/2, 5/5/3* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-32 and 34-57* is/are pending in the application.

4a) Of the above claim(s) *42-45 and 47-51* is/are withdrawn from consideration.

5)☒ Claim(s) *26-32,34,46 and 54-57* is/are allowed.

6)☒ Claim(s) *35-41,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
4) ☒ Interview Summary (PTO-413) of paper no. 25, dated 6/18/3 and 6/29/3.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

As discussed at the interview on April 11, 2003, the finality of the previous Office action is withdrawn and the amendments submitted November 4, November 12, 2002 and May 5, 2003 have been entered. All previous grounds of rejection are moot. However, a further search revealed the teachings of Heinen et al. (Journal of General Virology. 2002; 83: 1851-1859), which raises questions of the efficacy of the instant fusion protein as a vaccine composition. Therefore, new grounds of rejection are required.

Claims 26-32 and 34-57 are pending, claims 42-45 and 47-51 are withdrawn from consideration due to non-elected subject matter and claims 26-32, 34-41, 46 and 52-57 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-41, 52 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claim 35 encompasses a vaccine comprising an influenza virus fusion product comprising (i) an immunogenic extracellular part of an M2 membrane protein of a human influenza A virus, an NB protein of a human influenza B virus, or a CM2 protein of a human influenza C virus and (ii) a heterologous presenting carrier. Claims 36-39 state that the vaccine comprises the fusion product in isolated form, is anchored in the membrane in an acceptor cell or *Lactococci* cells expressing the fusion product or that the fusion product is a part of a lipid bilayer or cell wall. Claim 40 states that the vaccine further comprises at least one other

influenza virus antigen and claims 52 and 53 state that the vaccine comprises a cytokine or a vaccine antigen that is not Freund's adjuvant. Claim 41 is drawn to a method of making the vaccine by mixing it with an excipient.

The nature of the invention

The nature of the invention is drawn to treating and preventing any strain of influenza virus infection with the instant fusion protein as a vaccine, see page 6, lines 9-13 of the disclosure for example. Currently, influenza virus vaccines are updated yearly to prevent infection in prevalent strains. Due to the propensity of the virus to undergo mutations attributed to antigenic shift and antigenic drift, there are currently no known influenza virus vaccines that cross-protect against different strains of influenza viruses. See the top of the second column on page 1851 of Heinen et al. (Journal of General Virology. 2002; 83: 1851-1859).

The state of the prior art

The skilled artisan would doubt that the instant vaccine composition is therapeutic or prophylactic. Heinen et al. obtain purified M2eHBc from Sabine Neirynck, one of the inventors in the instant application, see the bullet in the second column on page 1852. Heinen et al. intramuscularly administer this fusion protein to pigs that are subsequently challenged with a field isolate, see the second bullet of the first column on page 1853. Heinen et al. report that "...clinical signs after challenge were more severe in all immunized groups compared with the control group", see the first sentence under the "Results" section and Figure 2 on page 1854. Heinen et al. also teach that there was no significant reduction in virus excretion, see the first full

paragraph in column 1 on page 1855. Heinen et al. conclude that while all of the vaccine compositions administered induced an antibody response to the extracellular portion of the M2 influenza virus A protein, no protection was observed upon challenge. Also, more severe clinical signs were manifested in vaccinated pigs compared to the control pigs. Heinen et al. state that while the art has speculated about achieving broad-spectrum immunity with the M2 protein, the data presented in pigs indicates that antibodies to the extracellular portion of M2 exacerbate disease, see the first paragraph of the discussion section.

Heinen et al. indicate that the data presented for pigs is in contrast to the results showing partial protection with the same construct in mice obtained in a previous study by Neirynck et al. (1999), see the discussion section bridging pages 1857-1858. Heinen et al. offer several explanations for the incongruency between the studies. One is that the sequence difference between the fusion protein and the challenge virus caused the absence of protection. Heinen et al. states that this indicates that the fusion protein is not cross protective against influenza viruses containing a swine influenza virus M2e sequence. Another explanation offered by Heinen et al. is the use of pigs versus the use of mice in the study conducted by Neirynck et al. Heinen et al. clearly indicate that pigs are a better model than mice to study influenza virus vaccination strategies for humans because they are a natural host of influenza virus infection, develop a similar course of disease manifestation upon infection and the same influenza virus strains can infect both pigs and humans. In addition, pigs have been implicated as mixing reservoirs of new influenza virus strains. See the discussion section bridging pages 1857-1858. Mice, in contrast, are naturally resistant to influenza virus infection, see the abstract and introduction of Thimme et al. (Virology. 1995; 211: 296-301).

Heinen et al. warns that "..clinical signs after infection should be observed more closely in further studies using M2 as an immunogen and caution should be exercised in using M2 in humans.", see the last full sentence of the paragraph bridging the columns on page 1857. Heinen et al. conclude that "[w]ays of inducing broad-spectrum immunity other than by vaccination with M2e...might be safer.", see the last paragraph on page 1858.

The level of one of ordinary skill

While it is within the skill for one in the art to construct the instant fusion protein, it is not within the skill for one to elicit a therapeutic or protective immune response with the fusion protein in a vaccine composition, as evidenced by the data of Heinen et al.

The level of predictability in the art

Heinen et al. discuss the difference between the exacerbation of disease generated in pigs with the instant construct and the partial protective efficacy observed in mice using the same construct in Neirynck et al. (1999), see the second full paragraph of the second column on page 1857. The fact that this same M2e fusion construct elicits contrasting immune reactions in two different animal models provides sufficient doubt that the construct is predictably efficacious in preventing influenza virus infection.

The assertion of a broad application encompassed by the instant vaccine claims necessarily requires evidence to support the therapeutic efficacy of the M2e fusion protein administered as a vaccine. As discussed by Heinen et al. on page 1857, influenza virus challenge in mice leads to lethal pulmonary infection, while pigs are naturally susceptible to influenza

virus infection and develop similar symptomology experienced by humans. The data of Heinen et al. clearly indicate that the instant fusion protein exacerbates disease in a natural swine host, see the previous citations. Therefore, the skilled artisan would predict that the M2e fusion protein would exacerbate disease in other natural hosts.

The amount of direction provided by the inventor

The specification teaches protection in mice administered using the fusion protein against challenge in the working examples. However, the specification does not provide sufficient guidance to enable the skilled artisan to elicit a protective immune response with the instant M2e fusion protein in an animal that is a natural host to influenza virus infections.

The existence of working examples

The disclosure presents a number of working examples using mice to demonstrate protection against influenza virus challenge, see page 42, lines 5-23 and page 44, line 36 to page 45, line 17 for example. However, as discussed by Heinen et al., mouse models are insufficient for evaluating potential influenza virus vaccines for a number of reasons, which are discussed above. The data provided in the working examples provides no nexus between the protection observed in mice and the proposed prophylactic effect as a vaccine in other hosts. This is clearly evident by the exacerbation of disease observed in pigs using the same fusion construct instantly claimed. The skilled artisan would be unable to effectively administer the fusion protein as a prophylactic vaccine from the teachings in the specification.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). There is no sufficient evidence presented in the disclosure to support the instant fusion protein as a vaccine composition. Heinen et al. teach that the instant fusion protein exacerbates disease in pigs. There is no correlative data provided in the specification that would enable the skilled artisan to achieve the same protective immune response observed in mice in other hosts. The skilled artisan would doubt that the instant vaccine is efficacious, as evidenced by the teachings of Heinen et al. The skilled artisan would also be unable to predict the effect the vaccine would have upon administration based upon the conflicting data generated in two animal models administered the instant construct. Therefore, it is concluded that an undue quantity of experimentation exists for the skilled artisan to use the instant influenza virus fusion protein as a vaccine.

Response to Arguments

In paper no. 24, applicant presents arguments refuting the teachings of Heinen et al. Applicant asserts that the data presented by Heinen et al. fail to support the conclusion that anti-M2e immunity exacerbates flu symptoms because the experimental controls were flawed. Applicant specifically argues that the empty plasmid "control" used in the reference is improper because none of the pigs received plasmid vaccination. Applicant argues that none of the pigs were administered negative controls of buffer or adjuvant alone or administered a conventional flu vaccine as a positive control.

Applicant's arguments as well as a careful review of the experimental procedures of Heinen et al. have been considered, but are found unpersuasive. It is first noted that contrary to applicant's summary of the experiment of Heinen et al., there was one experiment, not two. In the single experiment, one group of pigs received the instant fusion protein, M2eHBc, the second group received M2eHBc plus adjuvant, the third group was administered a plasmid expressing an influenza virus fusion protein that was designed by Heinen et al. and the fourth group received empty plasmid as a control. See the second bullet of the first column on page 1853 of Heinen et al.

The negative control of Heinen et al. is an empty plasmid, which is conventionally used in the art as a negative control. The plasmid has no similarity with the instant fusion protein obtained by Heinen et al. from one of the inventors, Sabine Neirynck. The empty plasmid does not contain any influenza virus epitope or any other feature that could possibly protect a host against influenza virus challenge. The absence of anti-influenza virus antibodies and the lack of lymphoproliferation in response to influenza virus antigens in the negative control group is

clearly demonstrated in Figures 3 and 4 of Heinen et al. Therefore, the empty plasmid used by Heinen et al. is a proper negative control.

As applicant notes in the last sentence of the second paragraph on page 5 of the response, Heinen et al. observed the highest fevers in pigs administered the empty plasmids post-challenge. The skilled artisan would expect more severe disease symptoms in a negative control group. The surprising finding from the data of Heinen et al. is that pigs administered fusion proteins that were supposed to protect against influenza virus challenge actually experienced worse clinical symptoms than the negative control group. This is surprising because the fusion protein construct instantly claimed had been previously shown to be protective in mice, see the first full paragraph of the first column on page 1852 of Heinen et al., which reviews the findings of the inventor. The fusion protein of Neirynck et al. was anticipated as a protective control because of its demonstrated efficacy as a vaccine in mice. This construct was used to evaluate the efficacy of a DNA construct expressing influenza virus proteins as a vaccine, see the last sentence of the introduction section on page 1852 of Heinen et al.

Applicant also states that a close review of Heinen et al. reveals that anti-M2e immunity did not exacerbate disease. Applicant bases this conclusion upon the data indicating a higher titer of M2e antibodies in the adjuvanted group than the non-adjuvanted group and the fact that the body temperature of the two groups after challenge was not statically different.

Applicant's arguments have been fully considered, but are found to be unpersuasive. A higher antibody titer has no bearing on the clinical signs of influenza virus infection actually observed. The clinical signs listed and evaluated by Heinen et al. are found in the first sentence under the "Results" section on page 1854. These include labored breathing, abdominal

breathing, anorexia, apathy and coughing. Heinen et al. conclude "unexpectedly, the clinical signs after challenge were more severe in all immunized groups compared to the control group", see the first sentence under the "Results" section and Figure 2. Further, Heinen et al. teach that "the mean temperatures in the different groups did not correlate with the clinical signs", see the last full sentence of the first column on page 1854, and that "no significant reduction in virus excretion was observed in the immunized groups compared with the control group", see the first sentence on page 1855.

Applicant's assertion that the observed titer of antibodies does not correlate with exacerbated clinical symptoms has been considered, but is found unpersuasive. Antibody levels generated by the different immunization groups are depicted in Figure 3. As shown, all of the fusion protein vaccine compositions elicit an antibody response and the negative control does not, as expected. The clinical signs observed after challenge clearly indicate that the instant fusion protein provides no protective efficacy in pigs because disease symptoms are equal to or greater than the negative control group, see Figure 2. This data clearly indicates that an antibody response to the instant fusion protein exacerbates disease in pigs.

Applicant also states that the lack of protective efficacy observed by Heinen et al. is due to the sequence mismatch between the human M2e in the fusion protein and the pig M2e sequence in the challenge virus. Applicant asserts that the M2e sequences are conserved within the same animal species and that the vaccine claimed is species-specific.

Applicant's arguments have been fully considered, but are found unpersuasive. The instant vaccine claims comprise an influenza virus fusion product comprising (i) an immunogenic extracellular part of an M2 membrane protein of a human influenza A virus, an

NB protein of a human influenza B virus, or a CM2 protein of a human influenza C virus and (ii) a heterologous presenting carrier. The claims do not require that the M2e portion of the fusion protein be species-specific to the animal administered the vaccine. Also, Heinen et al. discuss the sequencing differences between the fusion protein and the challenge virus administered in the first full paragraph of the second column on page 1857. Heinen et al. point out that antibodies induced by immunization bound to the amino acid sequence of the swine influenza challenge virus, indicating that the antibodies induced upon administration of the fusion protein are not species-specific. Heinen et al. proposes that immunization with the instant M2e fusion protein does not include viruses with the swine influenza virus M2e sequence. Heinen et al. also teach that pigs are a natural mixing reservoir for new pandemic strains in the same paragraph, which does not exclude the possibility of new influenza viruses comprising the swine influenza M2e sequence.

Applicant discusses a second experiment in Heinen et al. with administration of M2eNP DNA vaccination. However, there is only one experiment in the Heinen et al. reference. In the single experiment, one group of pigs received the instant fusion protein, M2eHBc, the second group received M2eHBc plus adjuvant, the third group was administered a plasmid expressing an influenza virus fusion protein that was designed by Heinen et al. and the fourth group received empty plasmid as a control. See the second bullet of the first column on page 1853 of Heinen et al.

The instant claims are drawn to a vaccine comprising a fusion protein. The results observed with the DNA vaccine construct of Heinen et al. is not relevant to the instant vaccine claims because the construct comprises influenza virus antigens that are presented differently to

the immune system and elicit a completely different immune response from a fusion protein vaccine, see the lymphoproliferative response in Figure 4 on page 1855 of Heinen et al.

Applicant disagrees that the pig model is a better animal model for studying the efficacy of influenza vaccines in mice. Applicant lists three vaccines that were first optimized in mice and later in human clinical trials.

Applicant's arguments have been fully considered, but are unpersuasive because the vaccines listed do not appear to have any similarity to the instant fusion protein vaccine claimed. Also, pigs and humans are a natural reservoir for influenza viruses, experience a similar course of disease symptomology and are naturally susceptible to influenza virus infection. Mice are not. Therefore, it is clearly evident that pigs are a reasonable animal model for studying potential influenza virus vaccines.

Allowable Subject Matter

Claims 26-32, 34, 46 and 54-57 are drawn to allowable subject matter. The prior art does not teach or suggest a fusion product comprising the extracellular portion of an influenza virus protein. In paper nos. 11 and 16, applicant clearly demonstrates that M2, NB and CM2 integral membrane proteins are equivalent in influenza A, B and C viruses, respectively. Applicant also clearly defines what an extracellular portion of a conserved influenza virus membrane protein comprises. The rejection against claim 46 is also obviated because of the "heterologous" carrier, which distinguishes this claim from a native M2 protein or a native M2 fusion protein. The influenza antigen "for an animal" in claims 54-57 are interpreted to mean that the influenza virus antigen is derived from a particular animal and is not interpreted to mean that the influenza virus antigen has therapeutic or prophylactic properties.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
July 2, 2003

JAMES HOUSEL 7/4/03
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